Pyrazolo[1, 4]diazepine-based small molecule oxytocin receptor partial agonists


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Background: Activation of the oxytocin receptor (OTR) can improve social symptoms in neurodevelopmental and psychiatric conditions that manifest asocial phenotypes, such as autism spectrum disorder and social anxiety disorder. Current OTR agonists, including the endogenous ligand oxytocin and the non-peptide ligand WAY-267,464, suffer from drawbacks such as poor brain uptake and lack of selectivity for the OTR over the structurally-related vasopressin 1a receptor (V1aR). We aimed to use molecular deconstruction to understand the moieties of WAY-267,464 that are important for selective OTR binding, in order to develop novel, selective, drug-like small molecule agonists of the OTR.

Methods: The 1-methyl-1,4,5,10-tetrahydrobenzo[b]pyrazolo[3,4-e][1,4]diazepine head group was synthesised as per (1,2), and amide derivatives were produced from carboxylic acid starting material proceeding via acid chloride intermediates. The affinity of these resulting ligands were measured using radioligand binding on membranes from HEK cells stably transfected with the human OTR and V1aR. These cells were also used to measure the potency and efficacy of the ligands using IP1 homogenous time-resolved fluorescence assays.

Results: Deconstruction of WAY-267,464 to the 3,4-dimethyl benzamide derivative produced a potent partial OTR agonist (EC50: 109 nM, efficacy: 6%) that was also a V1aR antagonist (IC50: 346 nM). Further deconstruction to both the 3-methyl benzamide and the unsubstituted benzamide derivative produced potent partial OTR agonists (3-methyl benzamide EC50: 407 nM, efficacy: 12%; unsubstituted benzamide EC50: 847 nM; efficacy: 12%) that lacked activity at the V1aR. Replacement of the phenyl group with bulky hydrophobic groups such as an adamantly group increased OTR efficacy but this was at the expense of potency (EC50: 4881 nM; efficacy: 33%). Replacement with cyclic hydrophobic groups such as a cycloheptyl group increased efficacy without loss of potency (EC50: 212 nM; efficacy: 55%).

Conclusions: Molecular deconstruction of WAY-267,464 produced potent and selective OTR agonists. Substitutions on the amide portion influenced potency and efficacy, revealing integral interactions of this moiety with the OTR.

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